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(57) Abstract

The invention relates to combinations of compounds having $5HT_{2C}$ and D_2 antagonist activity, compounds having activity at the two receptors, pharmaceutical compositions containing them, and their use in treating schizophrenia.

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PHARMACEUTICAL COMPOSITION CONTAINING A $5HT_{2C}$ ANTAGONIST AND A D_2 ANTAGONIST

The present invention relates to novel combinations of compounds, pharmaceutical compositions containing them, and their use in therapy.

WO 92/05170, WO 93/18028, WO 94/04533, WO 94/18170, WO 94/22871, WO 95/21844, WO 95/29177, WO 96/02537 and WO 96/23783 (all SmithKline Beecham plc) disclose heterocyclic derivatives which are described as possessing $5HT_{2C}$ receptor antagonist activity. These compounds are said to be of use in the treatment of various CNS disorders such as depression.

D_2-like antagonists such as haloperidol, raclopride and sulpiride are known in the art, for example see Seeman et al., Current Opinion in Neurology and Neurosurgery, (1993), **6**, 602 - 608.

It is now believed that administration of a combination of a $5HT_{2C}$ antagonist and a D_2 antagonist is likely to be much more effective in treating certain CNS disorders such as schizophrenia than administration of a single $5HT_{2C}$ or D_2 antagonist.

In a first aspect the present invention therefore provides a pharmaceutical composition for the treatment or prevention of CNS disorders which comprises:

- a compound having $5HT_{2C}$ antagonist activity;
- a compound having D_2 receptor antagonist activity; and
- a pharmaceutically acceptable carrier.

It will be understood that compounds having $5HT_{2C}$ or D_2 activity can usually be isolated in salt form and the invention extends to compositions in which the compounds are in salt form. Preferred salts are pharmaceutically acceptable salts, for example acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

The invention also extends to compositions in which the compounds are in stereoisomeric or tautomeric forms.

Preferred $5HT_{2C}$ antagonists include those disclosed in WO 92/05170, in particular the compound N-(1-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea (SB-200646). Another preferred compound is 5-methyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrollo[2,3-f]indole

(SB-206553) which is disclosed as Example 1 of WO 94/04533 and pharmaceutically acceptable salts thereof. Other preferred compounds are disclosed in WO96/23783 and in particular 1-[3-Fluoro-5-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline (Example 8, SB-228357). A particularly preferred $5HT_{2C}$ antagonist is 5-methyl-6-trifluoromethyl-1-[6-(2-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline (SB-243213) (which may also be called 2,3-dihydro-5-methyl-N-[2-(2-methyl-3-pyridinyl)oxy]-5-pyridinyl]-6-trifluoromethyl)-1H-indole-1-carboxamide) which is described as Example 1 in PCT/EP 97/03156. Other preferred $5HT_{2C}$ antagonists include those compounds disclosed in WO 93/18028, WO 94/04533, WO 94/18170, WO 94/22871, WO 95/21844, WO 95/29177, WO 96/02537, WO 96/23783.

Preferred D_2 antagonists include haloperidol, raclopride, sulpiride, ziprasidone, olanzapine, sertindole and quetiapine and pharmaceutically acceptable salts thereof.

The compounds having $5HT_{2C}$ and D_2 antagonist activity can be administered together or individually for the treatment of CNS disorders, that is to say either concurrently or non-concurrently.

As used herein, concurrently shall be understood to mean that the two agents are administered together or within 24 hours or less of each other, preferably within about 12 hours of each other, more preferably within about 1 hour of each other and most preferably within about 5 minutes of each other. Concurrent administration includes co-administration of separate dosage forms of the two agents or administration as a single dosage unit. Non-concurrently shall be taken to mean that the two agents are administered more than 24 hours apart.

In a further aspect of the present invention there is therefore provided a kit comprising in separate dosage forms a compound having $5HT_{2C}$ antagonist activity and a compound having D_2 antagonist activity. In particular, such kits are of use in providing to patients when administration of separate doses of the two active ingredients is required. Such kits can also be provided where sequential administration of the $5HT_{2C}$ antagonist and D_2 antagonist is required.

The invention also extends to pharmaceutical compositions comprising a compound having antagonist activity at both the $5HT_{2C}$ and D_2 receptors, that is to say a

single compound having dual activity, and a pharmaceutically acceptable carrier for the treatment or prevention of CNS disorders such as schizophrenia. The invention therefore provides a compound having antagonist activity at both the $5HT_{2C}$ and D_2 receptors for use in the treatment of CNS disorders such as schizophrenia.

The compositions of the present invention are expected to be of use in the treatment of CNS disorders disclosed in the above mentioned patent applications such as schizophrenia, mood disorders, including depression, seasonal effective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnestic disorders and age-associated memory impairment; and disorders of eating behaviours, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

Therefore in a further aspect the present invention provides a pharmaceutical composition which comprises a compound having $5HT_{2C}$ antagonist activity, a compound having D_2 antagonist activity, and a pharmaceutically acceptable carrier for use in therapy.

In another aspect the invention provides a pharmaceutical composition which comprises a compound having $5HT_{2C}$ antagonist activity, a compound having D_2 antagonist activity; and a pharmaceutically acceptable carrier in the manufacture of a medicament for the treatment of the aforementioned disorders.

In particular the invention provides a pharmaceutical composition which comprises a compound having $5HT_{2C}$ antagonist activity, a compound having D_2 antagonist activity; and a pharmaceutically acceptable carrier for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds and compositions according to the invention may advantageously be used in conjunction with one or more other therapeutic agents.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Compositions of the invention can also be administered in combination with other medicaments, for example conventional antidepressants or anxiolytics.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a

sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

Preferred compounds of the invention can be prepared according to the following examples.

Description 1

(5-Methoxy-2-nitro-4-trifluoromethylphenyl)acetonitrile (D1)

A mixture of 1-methoxy-4-nitro-2-trifluoromethylbenzene (93g, 0.421 mol) and 4-chlorophenoxyacetonitrile (77.55g, 0.463 mol) in dry DMF (500 ml) was added dropwise over 0.75 h to a stirred solution of KO^tBu (103.85g, 0.927 mol) in dry DMF (400 ml) at -10° C. After complete addition the resulting purple solution was maintained at -10° C for 1 h then poured into a mixture of ice/water (1.5 l) and 5 M aqueous HCl (1.5 l). The resulting mixture was extracted with dichloromethane (3 x 1 l). The combined extracts were washed with water (3 l), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on silica using 10-40% ethyl acetate/petroleum ether as eluant to give the crude product which was recrystallised from ethyl acetate/petroleum ether to afford the title compound (85.13g, 78%) as a white solid. Mp 103-104 °C.
^1H NMR ($CDCl_3$) δ: 4.10 (3H, s), 4.37 (2H, s), 7.34 (1H, s), 8.53 (1H, s).

Description 2

5-Methoxy-6-trifluoromethylindole (D2)

(5-Methoxy-2-nitro-4-trifluoromethylphenyl)acetonitrile (D1) (85g, 0.327 mol) in ethanol/water (9:1, 1.6 l) and glacial acetic acid (16 ml) was hydrogenated over 10% palladium on carbon (50 g) at 50 psi for 0.5 h at room temperature. The reaction mixture was filtered and evaporated *in vacuo*. The residue was partitioned between aqueous K_2CO_3 (1 l) and dichloromethane (2 x 1 l) and the combined organic extract was dried (Na_2SO_4) and evaporated to afford the title indole (67.63g, 96%) as a grey solid.
^1H NMR ($CDCl_3$) δ: 3.94 (3H, s), 6.53 (1H, m), 7.21 (1H, s), 7.32 (1H, m), 7.64 (1H, s), 8.25 (1H, br s).

Description 3

5-Methoxy-6-trifluoromethylindoline (D3)

The indole (D2) (67.63g, 0.315 mol) in glacial acetic acid (500 ml) was treated with sodium cyanoborohydride (40 g, 0.637 mol) portionwise at room temperature with stirring. After 3 h at room temperature the reaction mixture was diluted with water (500 ml) and basified with 40% aqueous NaOH with cooling. The mixture was then extracted with dichloromethane (3 x 500 ml) and the combined extracts were dried (Na_2SO_4) and evaporated to give the title compound (67.73g, 99%) as an off-white solid.
^1H NMR ($CDCl_3$) δ: 3.07 (2H, t), 3.58 (2H, t), 3.67 (1H, br s), 3.83 (3H, s), 6.83 (1H, s), 6.88 (1H, s).

Description 4

5-Hydroxy-6-trifluoromethylindoline (D4)

A mixture of 5-methoxy-6-trifluoromethylindoline (D3, 7.5g, 34.3 mmol) and iodotrimethylsilane (12.5 ml, 89.3 mmol) in dry chloroform (70 ml) was heated under reflux for 65 h. Methanol was then added cautiously with stirring to the cooled mixture, and solvent was then removed *in vacuo*. The residue was treated with saturated sodium bicarbonate solution and water until basic, and then extracted with dichloromethane/methanol. The organic extract was washed with brine, dried and evaporated. The residue was extracted with ether in a Soxhlet apparatus, and concentration

of the resultant solution gave the title compound in three crops (total 2.85g, 41%), m.p. > 180° (decomp.).

^{1}H NMR ($CDCl_3/CD_3OD$) δ: 3.02 (2H, d, J=8), 3.52 (2H, d, J=8), 4.00 (3H, s), 6.77 (1H, s), 6.83 (1H, s).

Description 5

1-Acetyl-5-hydroxy-6-trifluoromethylindoline (D5)

A mixture of indoline (D4, 2.84g, 14 mmol) and acetic anhydride (1.32 ml, 14 mmol) in dry dichloromethane (50 ml) was stirred at room temperature for 3h, then evaporated. The residue was treated cautiously with saturated sodium bicarbonate solution, then the solid product was filtered off, washed with water and dried to give the title compound (3.28g, 96%), m.p. 244-7°C.

^{1}H NMR (d_6-DMSO) δ: 2.10 (3H, s), 3.11 (2H, t, J=8), 4.06 (2H, t, J=8), 6.88 (1H, s), 8.18 (1H, s).

Description 6

1-Acetyl-6-trifluoromethyl-5-trifluoromethylsulphonyloxy-indoline (D6)

To a solution of the acetylindoline (D5, 1.19g, 4.9 mmol) in dry pyridine (10 ml) at 0°C was added trifluoromethanesulphonic anhydride (1.52g, 5.4 mmol). The mixture was then stirred overnight, while slowly warming to room temperature. The mixture was partially evaporated, the residual liquor was diluted well with water and the precipitate was filtered off. The crude product was dissolved in dichloromethane and the solution was washed with 1N hydrochloric acid and brine, dried and evaporated to give the title compound (1.77g, 96%).

^{1}H NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.32 (2H, t, J=8), 4.19 (2H, t, J=8), 7.29 (1H, s), 8.60 (1H, s).

MS m/z = 378 (MH^+)

Description 7

5-Methyl-6-trifluoromethylindoline (D7)

To a mixture of the trifluoromethylsulphonyloxyindoline (D6, 1.77g, 4.69 mmol), lithium chloride (0.60g, 14.1 mmol) and bis(triphenylphosphine) palladium (II) chloride (0.10g, 0.14 mmol) in dry dimethylformamide (15 ml) was added tetramethyltin (0.72 ml, 5.2 mmol). The mixture was heated at 110°C for 3.5h, then cooled and evaporated. The residue was partitioned between dichloromethane and water, and the organic phase was washed with brine, dried and evaporated. The crude product was dissolved in ethanol (30 ml), 10% aqueous sodium hydroxide solution (7.5 ml) and solid sodium hydroxide (1g) were added and the mixture was heated under reflux overnight. Ethanol was removed *in vacuo*, and the residue was diluted with water and extracted with dichloromethane. The organic extract was washed with brine, dried and evaporated. The residue was chromatographed on silica gel (50g), eluted under suction with 2:1 ether/petroleum ether to give the title compound (0.70g, 74%), m.p. 43-4°C.

^{1}H NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.02 (2H, t, J=8), 3.57 (2H, t, J=8), 3.78 (1H, broad), 6.85 (1H, s), 7.00 (1H, s).

Example 1

N-(1-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea

This compound can be prepared according to the procedure given in WO 92/05170.

Example 2

5-Methyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole

This compound can be prepared according to the procedure given in Example 1 of WO 94/04533.

Example 3

5-Methyl-6-trifluoromethyl-1-[6-(2-methylpyridin-3-yloxy)-pyridin-3-ylcarbamoyl]indoline

A mixture of indoline (D7, 20g, 99.5 mmol), phenylcarbamate (D10, 31.9g, 99.5 mmol) and triethylamine (13.9 ml, 100 mmol) in dry dimethylformamide (1L) was heated at 95-105°C for 1 h, then cooled and evaporated *in vacuo*. The residue was diluted with dichloromethane and washed with 10% aqueous sodium hydroxide, with addition of methanol to keep the product in solution. The organic phase was washed with water and brine, dried and evaporated. The crude product was recrystallised from dichloromethane to give the title compound (32.5g, 76%), m.p. 112-4°C.

The hydrochloride can be prepared by treating a solution of the free base in methanol or propanol with concentrated hydrochloric acid.

Activity is assessed by the reversal of haloperidol-induced catalepsy in the rat (bar method).

A metal bar 10cm high x 10mm diameter is suspended between two upright posts, and the bar is divided into compartments with card or perspex partitions. Groups of rats are dosed intraperitoneally with a range of doses of the test compound or vehicle. The rats are positioned so that their hind legs contact the ground and their forelegs are draped over the horizontal bar. The measure of catalepsy is taken as the time taken for the rat to remove the front paws from the bar, with a maximum measurement of 120 seconds and the test is repeated at 30, 60 and 90 minutes. To assess the reversal of catalepsy rats are administered vehicle or haloperidol (3umol/kg ip) and tested for catalepsy at 30 and 60 minutes in the standard manner; the rats are then injected with a range of doses of the test compound and are tested for catalepsy 30 minutes later.

SB-228357 significantly reversed haloperidol-induced catalepsy at doses of 0.32, 3.2 and 10 mg/kg po. SB-243213 (0.1-10 mg/kg po) significantly reversed haloperidol-induced catalepsy. The 5HT2B antagonist, SB-215505 (0.1-3.2 mg/kg po) and the 5HT2A antagonist, MDL-100907 (0.003-3.2 mg/kg po) did <u>not</u> reverse haloperidol-induced catalepsy.

CLAIMS:

1. A pharmaceutical composition for the treatment or prevention of CNS disorders which comprises:

- a compound having $5HT_{2C}$ antagonist activity;
- a compound having D_2 antagonist activity; and
- a pharmaceutically acceptable carrier.

2. A composition according to claim 1 in which the $5HT_{2C}$ antagonist is: N-(1-methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea or 5-methyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrollo[2,3-f]indole or a pharmaceutically acceptable salts thereof.

3. A composition according to claim 1 in which the $5HT_{2C}$ antagonist is 5-methyl-6-trifluoromethyl-1-[6-(2-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline

4. A composition according to any of claims 1 to 3 in which the D2 antagonist is haloperidol, raclopride and sulpiride or pharmaceutically acceptable salts thereof.

5. A composition according to any of claims 1 to 3 in which the D2 antagonist is ziprasidone, olanzapine, sertindole and quetiapine or pharmaceutically acceptable salts thereof.

6. A pharmaceutical composition comprising a compound having antagonist activity at both the $5HT_{2C}$ and D_2 receptors and a pharmaceutically acceptable carrier.

7. A composition according to any one of claims 1 to 6 for use in the treatment or prevention of schizophrenia.

8. A compound having antagonist activity at both the $5HT_{2C}$ and D_2 receptors for use in the treatment of CNS disorders such as schizophrenia

9. A kit comprising a dosage unit containing a $5HT_{2C}$ antagonist or a pharmaceutically acceptable salt thereof and a dosage unit containing a D_2 antagonist or a pharmaceutically acceptable salt thereof.